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Mary Hale, Information Branch Supervisor
308-4258, CM1-1E01

Voluntary Results Feedback Form

➤ I am an examiner in Workgroup: Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

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=> s 223222-27-8/RN

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=> file RN

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SESSION

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STRUCTURE FILE UPDATES: 29 JUL 2003 HIGHEST RN 557055-78-4

DICTIONARY FILE UPDATES: 29 JUL 2003 HIGHEST RN 557055-78-4

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

ENTER DISPLAY FORMAT (IDE):all

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
 RN 223122-27-8 REGISTRY
 CN D-Glutamic acid, N2-[[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-L-arginyl-(2R)-
 2-piperidinecarbonylglycylglycyl-(.alpha.S)-.alpha.-
 aminobenzenebutanoylglycyl-.beta.-alaninyl-L-.alpha.-aspartyl-L-tyrosyl-L-
 .alpha.-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-L-.alpha.-glutamyl-L-
 .alpha.-glutamyl-L-alanyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
 FS PROTEIN SEQUENCE; STEREOSEARCH
 SQL 18
 NTE modified (modifications unspecified)

type	location	description
uncommon	Pip-2	-
uncommon	Abu-5	-
uncommon	Bal-7	-
modification	Arg-1	undetermined modification
modification	Abu-5	phenyl<Ph>
modification	Ala-17	cyclohexyl<Chx>

SEQ 1 RXGGXGXDYB PIPEEAAE

SEQ3 1 Arg-Pip-Gly-Gly-Abu-Gly-Bal-Asp-Tyr-Glu-
 11 Pro-Ile-Pro-Glu-Glu-Ala-Ala-Glu

RELATED SEQUENCES AVAILABLE WITH SEQLINK

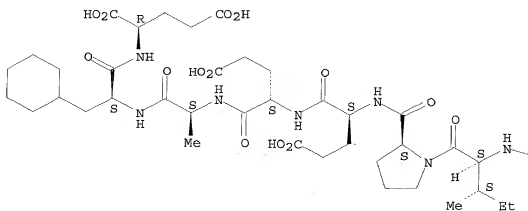
MF C102 H147 N21 O32 S
 SR CA
 LC STN Files: CA, CAPLUS

Ring System Data

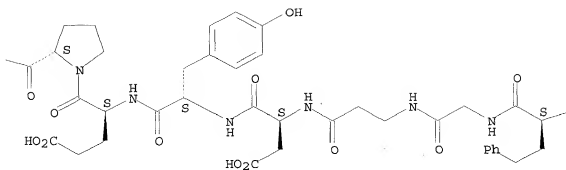
Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C4N	NC4	5	C4N	16.136.1	2
C6	C6	6	C6	46.150.1	1
C6	C6	6	C6	46.150.18	3
C5N	NC5	6	C5N	46.156.1	1

Absolute stereochemistry.

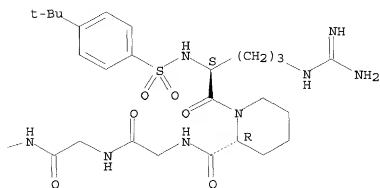
PAGE 1-A



PAGE 1-B



PAGE 1-C



2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1

AN 132:262009 CA
TI Design of P1' and P3' Residues of Trivalent Thrombin Inhibitors and Their
Crystal Structures
AU Slon-Usakiewicz, Jacek J.; Sivaraman, J.; Li, Yunge; Cygler, Mirosław;
Konishi, Yasuo
CS Biotechnology Research Institute, National Research Council of Canada,
Montreal, QC, H4P 2R2, Can.
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English

CC 7-3 (Enzymes)
 Section cross-reference(s): 75

AB Synthetic bivalent thrombin inhibitors comprise an active site blocking segment, a fibrinogen recognition exosite blocking segment, and a linker connecting these segments. Possible nonpolar interactions of the P1' and P3' residues of the linker with thrombin S1' and S3' subsites, resp., were identified using the "Methyl Scan" method [Slon-Usakiewicz et al. (1997) Biochem. 36, 13494-13502]. A series of inhibitors (4-tert-butylbenzenesulfonyl)-Arg-(D-pipecolic acid)-Xaa-Gly-Yaa-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-(.beta.-cyclohexylalanine)-(D-Glu)-OH, in which nonpolar P1' residue Xaa or P3' residue Yaa was incorporated, were designed and improved the affinity to thrombin. Substitution of the P3' residue with D-phenylglycine or D-Phe improved the Ki value to (9.5 +/- 0.6) .times. 10-14 or 1.3 +/- 0.5 .times. 10-13 M, resp., compared to that of a ref. inhibitor with Gly residues at Xaa and Yaa residues (Ki = (2.4 +/- 0.5) .times. 10-11 M). Similarly, substitution of the P1' residue with L-norleucine or L-.beta.-(2-thienyl)alanine lowered the Ki values to (8.2 +/- 0.6) .times. 10-14 or (5.1 +/- 0.4) .times. 10-14 M, resp. The linker Gly-Gly-.beta.-Ala of the inhibitors in the previous sentence was simplified with 12-aminododecanoic acid, resulting in further improvement of the Ki values to (3.8 +/- 0.6) .times. 10-14 or (1.7 +/- 0.4) .times. 10-14 M, resp. These Ki values are equiv. to that of natural hirudin (2.2 .times. 10-14 M), yet the size of the synthetic inhibitors (2 kD) is only one-third that of hirudin (7 kD). Two inhibitors, with L-norleucine or L-.beta.-(2-thienyl)alanine at the P1' residue and the improved linker of 12-aminododecanoic acid, were crystd. in complex with human .alpha.-thrombin. The crystal structures of these complexes were solved and refined to 2.1 .ANG. resoln. The Lys60F side chain of thrombin moved significantly and formed a large nonpolar S1' subsite to accommodate the bulky P1' residue.

ST trivalent thrombin inhibitor design crystal structure

IT Enzyme functional sites
 (active; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT Enzyme kinetics
 (of inhibition; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT Crystal structure
 (of trivalent thrombin inhibitors complexed with thrombin)

IT Structure-activity relationship
 (thrombin-inhibiting; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT 9002-04-4D, Thrombin, complexes with trivalent thrombin inhibitors 263367-63-1D, complexes with thrombin 263367-64-2D, complexes with thrombin

RL: PRP (Properties)
 (crystal structure; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT 197518-05-1 197518-06-2 197518-07-3 197518-08-4 197519-06-5
 223117-53-1 223117-64-4 223117-70-2 223117-75-7 223117-81-5
 223117-89-3 223117-95-1 223118-14-7 223118-20-5 223118-31-8
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 223118-76-1 223118-82-9 223118-88-5 223119-00-4 223119-13-9
 223119-22-0 223119-28-6 223119-36-6 223119-45-7 223119-53-7
 223119-62-8 223119-72-0 223119-78-6 223119-87-7 223119-93-5
 223120-02-3 223120-12-5 223120-26-1 223120-49-8 223120-63-6
 223120-68-1 223120-74-9 223120-84-1 223120-90-9 223120-97-6
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 223122-06-3 223122-18-7 223122-23-4 223122-27-8 223122-31-4
 223122-37-0 223122-44-9 223122-52-9 223122-63-2 223122-72-3
 223122-83-6 263367-65-3 263367-66-4 263367-67-5 263367-68-6
 263367-69-7 263367-70-0 263367-74-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PRP (Properties); BIOL (Biological study)
 (design of P1' and P3' residues of trivalent thrombin inhibitors and
 their crystal structures)

IT 9002-04-4, Thrombin
 RU: BPR (Biological process); BSU (Biological study, unclassified); PRP
 (Properties); BIOL (Biological study); PROC (Process)
 (design of P1' and P3' residues of trivalent thrombin inhibitors and
 their crystal structures)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

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REFERENCE 2

AN 130:297001 CA
 TI Preparation of trivalent thrombin inhibitors
 IN Konishi, Yasuo; Slon, Jacek
 PA National Research Council of Canada, Can.
 SO PCT Int. Appl., 46 pp.
 CODEN: P1XXD2

DT Patent
 LA English
 IC ICM C07K014-815
 ICS A61K038-58

CC 34-3 (Amino Acids, Peptides, and Proteins)
 section cross-reference(s): 1, 7

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9919356	A1	19990422	WO 1997-CA745	19971015
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	AU 9746122	A1	19990503	AU 1997-46122	19971015
	AU 761011	B2	20030529		
	EP 1023324	A1	20000802	EP 1997-944656	19971015
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NZ 503669	A	20010928	NZ 1997-503669	19971015
	JP 2001519442	T2	20011023	JP 2000-515927	19971015
PRAI	WO 1997-CA745		19971015		
AB	Trivalent thrombin inhibitors AS-Z-P (AS represents an S subsite blocking segment, P represents a fibrinogen recognition exosite blocking segment, Z represents a S' subsite blocking segment) or their pharmaceutically acceptable salts, were prepd. The S' subsite blocking segment, besides binding to the thrombin S' subsites, connects the S subsite blocking segment and the fibrinogen recognition exosite blocking segment. This binding of Z segment together with the bindings of the AS and P segments, contributes to improve the affinity of the inhibitors significantly. The AS blocking segment and the P segment preferably have the sequence Bbs-Arg-D-Pip- (Bbs = 4-tert-butylbenzenesulfonyl, Pip = pipercolic acid) and Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH (Cha = .beta.-cyclohexylalanine), resp. The Z segment preferably has the sequence Xaa-Gly-Yaa-Gly-.beta.-Ala where: Xaa, Yaa = Gly, Ala, D-Ala, Val, D-Val, Phe, D-Phe, His, D-His, Nva, D-Nva, Ile, D-Ile, Nle, D-Nle, .alpha.Aib (2-aminoisobutyric acid), Phg (phenylglycine), D-Phg, Thi (.beta.- (2-thienyl)alanine), D-Thi, Chg (cyclohexylglycine), etc. Thus, Bbs-Arg-D-Pip-Thi-Gly-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH, having a Ki value of 0.051 +/- 0.004 pM, was prepd. by the solid phase method using a conventional Fmoc procedure. The preferred inhibitors have Ki values smaller than 1 pM and are useful for treating or preventing vascular diseases.				
ST	peptide prepn trivalent thrombin inhibitor				
IT	Peptides, preparation				
	RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)				
	(prepn. of trivalent thrombin inhibitors)				
IT	Blood vessel, disease				
	(treatment of; prepn. of trivalent thrombin inhibitors)				
IT	9002-04-4, Thrombin				
	RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; prepn. of trivalent thrombin inhibitors)				
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	223121-54-8P	223121-58-2P	223121-63-9P	223121-68-4P	223121-74-2P
	223121-81-1P	223121-88-8P	223121-94-6P	223122-01-8P	223122-06-3P

223122-18-7P 223122-23-4P 223122-27-8P 223122-31-4P 223122-37-0P
223122-44-9P 223122-52-9P 223122-63-2P 223122-72-3P 223122-83-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent thrombin inhibitors)

IT 9002-04-4, Thrombin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(.alpha.-; prepn. of trivalent thrombin inhibitors)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

- (1) Konishi, Y; WO 9511921 A 1995 CAPLUS
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FILE LAST UPDATED: 29 Jul 2003 (20030729/ED)

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=> s 223122-27-8

REGISTRY INITIATED

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L5 2 L4

=> d all

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:94674 CAPLUS
DN 132:262009
TI Design of P1' and P3' Residues of Trivalent Thrombin Inhibitors and Their Crystal Structures
AU Slon-Usakiewicz, Jacek J.; Sivaraman, J.; Li, Yunge; Cygler, Mirosław; Konishi, Yasuo
CS Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P 2R2, Can.
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English

CC 7-3 (Enzymes)
 Section cross-reference(s): 75

AB Synthetic bivalent thrombin inhibitors comprise an active site blocking segment, a fibrinogen recognition exosite blocking segment, and a linker connecting these segments. Possible nonpolar interactions of the P1' and P3' residues of the linker with thrombin S1' and S3' subsites, resp., were identified using the "Methyl Scan" method [Slon-Usakiewicz et al. (1997) Biochem. 36, 13494-13502]. A series of inhibitors (4-tert-butylbenzenesulfonyl-Arg-(D-pipecolic acid)-Xaa-Gly-Yaa-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-(.beta.-cyclohexylalanine)-(D-Glu)-OH, in which nonpolar P1' residue Xaa or P3' residue Yaa was incorporated, were designed and improved the affinity to thrombin. Substitution of the P3' residue with D-phenylglycine or D-Phe improved the Ki value to (9.5 +/- 0.6) .times. 10-14 or 1.3 +/- 0.5 .times. 10-13 M, resp., compared to that of a ref. inhibitor with Gly residues at Xaa and Yaa residues (Ki = (2.4 +/- 0.5) .times. 10-11 M). Similarly, substitution of the P1' residue with L-norleucine or L-.beta.-(2-thienyl)alanine lowered the Ki values to (8.2 +/- 0.6) .times. 10-14 or (5.1 +/- 0.4) .times. 10-14 M, resp. The linker Gly-Gly-.beta.-Ala of the inhibitors in the previous sentence was simplified with 12-aminododecanoic acid, resulting in further improvement of the Ki values to (3.8 +/- 0.6) .times. 10-14 or (1.7 +/- 0.4) .times. 10-14 M, resp. These Ki values are equiv. to that of natural hirudin (2.2 .times. 10-14 M), yet the size of the synthetic inhibitors (2 kD) is only one-third that of hirudin (7 kD). Two inhibitors, with L-norleucine or L-.beta.-(2-thienyl)alanine at the P1' residue and the improved linker of 12-aminododecanoic acid, were crystd. in complex with human .alpha.-thrombin. The crystal structures of these complexes were solved and refined to 2.1 .ANG. resolu. The Lys60F side chain of thrombin moved significantly and formed a large nonpolar S1' subsite to accommodate the bulky P1' residue.

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IT 9002-04-4D, Thrombin, complexes with trivalent thrombin inhibitors 263367-63-1D, complexes with thrombin 263367-64-2D, complexes with thrombin

RL: PRP (Properties)
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IT 197518-05-1 197518-06-2 197518-07-3 197518-08-4 197519-06-5
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 223120-68-1 223120-74-9 223120-84-1 223120-90-9 223120-97-6
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 223121-68-4 223121-74-2 223121-88-8 223121-94-6 223122-01-8
 223122-06-3 223122-18-7 223122-23-4 223122-27-8
 223122-31-4 223122-37-0 223122-44-9 223122-52-9 223122-63-2
 223122-72-3 223122-83-6 263367-65-3 263367-66-4 263367-67-5
 263367-68-6 263367-69-7 263367-70-0 263367-74-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PRP (Properties); BIOL (Biological study)
 (design of P1' and P3' residues of trivalent thrombin inhibitors and
 their crystal structures)

IT 9002-04-4, Thrombin
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP
 (Properties); BIOL (Biological study); PROC (Process)
 (design of P1' and P3' residues of trivalent thrombin inhibitors and
 their crystal structures)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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=> d 11 1-2 ibib abs

L1 HAS NO ANSWERS

L1 O SEA FILE=REGISTRY ABB=ON PLU=ON 223222-27-8/RN

=> s 223122-27-8

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L7 2 L6

=> d 17 1-2 ibib abs

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000.94674 CAPLUS
DOCUMENT NUMBER: 132:262009
TITLE: Design of P1' and P3' Residues of Trivalent Thrombin Inhibitors and Their Crystall Structures
AUTHOR(S): Slon-Usakiewicz, Jacek J.; Sivaraman, J.; Li, Yunge; Cygler, Mirosław; Konishi, Yasuo
CORPORATE SOURCE: Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P 2R2, Can.
SOURCE: Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Synthetic bivalent thrombin inhibitors comprise an active site blocking segment, a fibrinogen recognition exosite blocking segment, and a linker connecting these segments. Possible nonpolar interactions of the P1' and P3' residues of the linker with thrombin S1' and S3' subsites, resp., were identified using the "Methyl Scan" method [Slon-Usakiewicz et al. (1997) Biochem. 36, 13494-13502]. A series of inhibitors (4-tert-butylbenzenesulfonyl)-Arg-(D-pipecolic acid)-Xaa-Gly-Yaa-Gly-.beta.Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-(.beta.-cyclohexylalanine)-(D-Glu)-OH, in which nonpolar P1' residue Xaa or P3' residue Yaa was incorporated, were designed and improved the affinity to thrombin. Substitution of the P3' residue with D-phenylglycine or D-Phe improved the Ki value to (9.5 .+- .0.6) .times. 10-14 or 1.3 .+- .0.5 .times. 10-13 M, resp., compared to that of a ref. inhibitor with Gly residues at Xaa and Yaa residues (Ki = (2.4 .+- .0.5) .times. 10-11 M). Similarly, substitution of the P1' residue with L-norleucine or L-.beta.-(2-thienyl)alanine lowered the Ki values to (8.2 .+- .0.6) .times. 10-14 or (5.1 .+- .0.4) .times. 10-14 M, resp. The linker Gly-Gly-Gly-.beta.Ala of the inhibitors in the previous sentence was simplified with 12-aminododecanoic acid, resulting in further improvement of the Ki values to (3.8 .+- .0.6) .times. 10-14 or (1.7 .+- .0.4) .times. 10-14 M, resp. These Ki values are equiv. to that of natural hirudin (2.2 .times. 10-14 M), yet the size of the synthetic inhibitors (2 kD) is only one-third that of hirudin (7 kD). Two inhibitors, with L-norleucine or L-.beta.-(2-thienyl)alanine at the P1' residue and the improved linker of 12-aminododecanoic acid, were crystd. in complex with human .alpha.-thrombin. The crystal structures of these complexes were solved and refined to 2.1 .ANG. resolu. The Lys60F side chain of thrombin moved significantly and formed a large nonpolar S1' subsite to accommodate the bulky P1' residue.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:271384 CAPLUS
DOCUMENT NUMBER: 130:297001
TITLE: Preparation of trivalent thrombin inhibitors
INVENTOR(S): Konishi, Yasuo; Slon, Jacek
PATENT ASSIGNEE(S): National Research Council of Canada, Can.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9919356	A1	19990422	WO 1997-CA745	19971015
W:	AL, AM, AT, AU, AZ, BA, BE, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IR, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9746122	A1	19990503	AU 1997-46122	19971015
AU 761011	B2	20030529		
EP 1023324	A1	20000802	EP 1997-944656	19971015
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
NZ 503669	A	20010928	NZ 1997-503669	19971015
JP 2001519442	T2	20011023	JP 2000-515927	19971015
PRIORITY APPLN. INFO.:			WO 1997-CA745	A 19971015
OTHER SOURCE(S):	MARPAT 130:297001			
AB	<p>Trivalent thrombin inhibitors AS-Z-P (AS represents an S subsite blocking segment, P represents a fibrinogen recognition exosite blocking segment, Z represents a S' subsite blocking segment) or their pharmaceutically acceptable salts, were prepd. The S' subsite blocking segment, besides binding to the thrombin S' subsites, connects the S subsite blocking segment and the fibrinogen recognition exosite blocking segment. This binding of Z segment together with the bindings of the AS and P segments, contributes to improve the affinity of the inhibitors significantly. The AS blocking segment and the P segment preferably have the sequence Bbs-Arg-D-Pip- (Bbs = 4-tert-butylbenzenesulfonyl, Pip = pipecolic acid) and Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH (Cha = .beta.-cyclohexylalanine), resp. The Z segment preferably has the sequence Xaa-Gly-Yaa-Gly-.beta.-Ala where: Xaa, Yaa = Gly, Ala, D-Ala, Val, D-Val, Phe, D-Phe, His, D-His, Nva, D-Nva, Ile, D-Ile, Nle, D-Nle, .alpha.-Aib (2-aminoisobutyric acid), Phg (phenylglycine), D-Phg, Thi (.beta.- (2-thienyl)alanine), D-Thi, Chg (cyclohexylglycine), etc. Thus, Bbs-Arg-D-Pip-Thi-Gly-Gly-Gly-.beta.-Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH, having a Ki value of 0.051 +/- 0.004 pM, was prepd. by the solid phase method using a conventional Fmoc procedure. The preferred inhibitors have Ki values smaller than 1 pM and are useful for treating or preventing vascular diseases.</p>			
REFERENCE COUNT:	4	THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

=> d 17 1-2 so it

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICAW; ISSN: 0006-2960

IT Enzyme functional sites
(active; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT Enzyme kinetics
(of inhibition; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT Crystal structure
(of trivalent thrombin inhibitors complexed with thrombin)

IT Structure-activity relationship
(thrombin-inhibiting; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT 9002-04-4D, Thrombin, complexes with trivalent thrombin inhibitors
263367-63-1D, complexes with thrombin 263367-64-2D, complexes with thrombin

RL: PRP (Properties)

(crystal structure; design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

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	223117-53-1	223117-64-4	223117-70-2	223117-75-7	223117-81-5
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	223122-06-3	223122-18-7	223122-23-4	223122-27-8	
	223122-31-4	223122-37-0	223122-44-9	223122-52-9	223122-63-2
	223122-72-3	223122-83-6	263367-65-3	263367-66-4	263367-67-5
	263367-68-6	263367-69-7	263367-70-0	263367-74-4	

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

IT 9002-04-4, Thrombin

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(design of P1' and P3' residues of trivalent thrombin inhibitors and their crystal structures)

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN

SO PCT Int. Appl., 46 pp.

CODEN: PIXXD2

IT Peptides, preparation

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent thrombin inhibitors)

IT Blood vessel, disease

(treatment of; prepn. of trivalent thrombin inhibitors)

IT 9002-04-4, Thrombin

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; prepn. of trivalent thrombin inhibitors)

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	223119-07-1P	223119-13-9P	223119-22-0P	223119-28-6P	223119-36-6P
	223119-45-7P	223119-53-7P	223119-62-8P	223119-72-0P	223119-78-6P
	223119-87-7P	223119-93-5P	223120-02-3P	223120-12-5P	223120-26-1P
	223120-49-8P	223120-63-6P	223120-68-1P	223120-74-9P	223120-84-1P
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	223121-81-1P	223121-88-8P	223121-94-6P	223122-01-8P	223122-06-3P
	223122-18-7P	223122-23-4P	223122-27-8P	223122-31-4P	
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	223122-83-6P				

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of trivalent thrombin inhibitors)

IT 9002-04-4, Thrombin

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(.alpha.-; prepn. of trivalent thrombin inhibitors)

=> S 22322-27-8
L8 0 22322-27-8

=> S 223122-27-8

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or PHITSTR) to directly view retrieved structures.

L10 2 L9

=> D L10 1-2 SO

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> S 223121-63-9

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or PHITSTR) to directly view retrieved structures.

L12 2 L11

=> D L12 1-2 SO

L12 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> S 223121-04-8

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or PHITSTR) to directly view retrieved structures.

L14 1 L13

=> D L14 SO

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> S 223119-87-7

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L16 2 L15

=> D L16 1-2 SO

L16 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L16 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> S 223119-07-1

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L18 1 L17

=> D L18 so

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> s 223118-31-8

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L20 2 L19

=> d 120 1-2 so

L20 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L20 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> s 223117-53-1

Registry INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L22 2 L21

=> d 122 1-2 so

L22 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

=> s 197518-05-1

Registry INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L24 3 L23

=> d 124 1-3 so

L24 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (2000), 39(9), 2384-2391
CODEN: BICHAW; ISSN: 0006-2960

L24 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

L24 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
SO Biochemistry (1997), 36(44), 13494-13502
CODEN: BICHAW; ISSN: 0006-2960

=> d his

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L1 FILE 'REGISTRY' ENTERED AT 13:53:42 ON 30 JUL 2003
L2 0 S 223222-27-8/RN
1 S 223122-27-8
SET SMA OFF
L3 0 S CAPLUS

FILE 'CAPLUS' ENTERED AT 14:22:08 ON 30 JUL 2003
S 223122-27-8/REG#

L4 FILE 'REGISTRY' ENTERED AT 14:22:27 ON 30 JUL 2003
1 S 223122-27-8/RN

L5 FILE 'CAPLUS' ENTERED AT 14:22:28 ON 30 JUL 2003
2 S L4
S 223122-27-8/REG#

L6 FILE 'REGISTRY' ENTERED AT 14:23:55 ON 30 JUL 2003
1 S 223122-27-8/RN

L7 FILE 'CAPLUS' ENTERED AT 14:23:55 ON 30 JUL 2003
2 S L6
L8 0 S 223222-27-8
S 223122-27-8/REG#

L9 FILE 'REGISTRY' ENTERED AT 14:29:58 ON 30 JUL 2003
1 S 223122-27-8/RN

L10 FILE 'CAPLUS' ENTERED AT 14:29:59 ON 30 JUL 2003
2 S L9
S 223121-63-9/REG#

L11 FILE 'REGISTRY' ENTERED AT 14:31:03 ON 30 JUL 2003
1 S 223121-63-9/RN

L12 FILE 'CAPLUS' ENTERED AT 14:31:04 ON 30 JUL 2003
2 S L11
S 223121-04-8/REG#

L13 FILE 'REGISTRY' ENTERED AT 14:31:42 ON 30 JUL 2003
1 S 223121-04-8/RN

L14 FILE 'CAPLUS' ENTERED AT 14:31:42 ON 30 JUL 2003
1 S L13
S 223119-87-7/REG#

L15 FILE 'REGISTRY' ENTERED AT 14:32:07 ON 30 JUL 2003
1 S 223119-87-7/RN

L16 FILE 'CAPLUS' ENTERED AT 14:32:08 ON 30 JUL 2003
2 S L15
S 223119-07-1/REG#

L17 FILE 'REGISTRY' ENTERED AT 14:32:31 ON 30 JUL 2003
1 S 223119-07-1/RN

L18 FILE 'CAPLUS' ENTERED AT 14:32:32 ON 30 JUL 2003
1 S L17
S 223118-31-8/REG#

L19 FILE 'REGISTRY' ENTERED AT 14:32:56 ON 30 JUL 2003
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 2 S L19
 S 223117-53-1/REG#

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 1 S 223117-53-1/RN

L22 FILE 'CAPLUS' ENTERED AT 14:33:25 ON 30 JUL 2003
 2 S L21
 S 197518-05-1/REG#

L23 FILE 'REGISTRY' ENTERED AT 14:33:56 ON 30 JUL 2003
 1 S 197518-05-1/RN

L24 FILE 'CAPLUS' ENTERED AT 14:33:56 ON 30 JUL 2003
 3 S L23

=> SEL RAN.CAPLUS(1) L2 1

NO ANSWERS SELECTED. THE ANSWER SET WAS CREATED IN FILE 'REGISTRY'.
 USE THE FILE COMMAND TO CHANGE TO THE CORRECT FILE.
 An answer set can be processed to create terms only
 in the same file in which it was created.

=> SET SMA ON

SET COMMAND COMPLETED

=> SEL RAN.CAPLUS(1) L2 1

SmartSELECT INITIATED

New TRANSFER and ANALYZE Commands Now Available
 See HELP TRANSFER and HELP ANALYZE for Details

NO ANSWERS SELECTED. THE ANSWER SET WAS CREATED IN FILE 'REGISTRY'.
 USE THE FILE COMMAND TO CHANGE TO THE CORRECT FILE.
 An answer set can be processed to create terms only
 in the same file in which it was created.

=>

=> FIL

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	7.67	92.81
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-2.57

FILE 'HOME' ENTERED AT 14:37:56 ON 30 JUL 2003

=> SEL RAN.CAPLUS(1) L2 1

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
 Some commands only work in certain files. For example, the EXPAND
 command can only be used to look at the index in a file which has an
 index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
 commands which can be used in this file.

=>